X-D. Experimental Atherosclerosis

In the course of investigating the toxicity of nicotine, Adler and Hensel (1906) discovered lesions in the aorta of rabbits. The lesions were degenerative and aneurysmal; they were similar to those induced by epinephrine and unlike the human form of atherosclerosis. Degenerative lesions were later seen in rabbits by Grosgogeat and Roubelakis (1965) and Lellouch et al. (1968) and in dogs by Hueper (1943) but were not seen in rats by Thienes (1960). The chronic administration of nicotine alone caused a transient increase in blood lipids but the level approximated the control level towards the end of the experiment (Schivelbein et al., 1970). Although the calcium controls of the aorta of nicotine-treated rabbits was increased, there were no differences in histological changes in the blood vessels between nicotine-treated and control rabbits.

The rabbit has been the favorite animal for experimental induction of atherosclerosis. The initial attempt of Wenzel et al. (1959) failed to establish an increase in severity of atherosclerosis in rabbits on a high cholesterol diet. Two other groups reported an increase in extent of dietary-induced atherosclerosis in nicotine-treated rabbits—one group from Chicago (Haas et al., 1966a, 1966b, 1968; Landerholm et al., 1967) and another group from Boston (Stefanovich et al., 1969). The oxygen uptake of tissues from hypercholesterolemic rabbits has been reported to be more sensitive to the depressant action of nicotine than that of tissues from

normocholesterolemic rabbits (Adachi et al., 1965). Nicotine was shown to change the lipid patterns of the perfused dog aorta and coronary artery (Kupke, 1972). The results were regarded by the author as supporting the hypothesis that nicotine may impair oxidative enzymes by damaging the mitochondrial structures, thereby leading to lipid accumulation. Experiments on the atherosclerotic dog aorta and the human aorta are needed.

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X-E. Experimental Hyperlipidemias

Epinephrine is known to mobilize free fatty acids from fatty tissue and this was followed by elevation of cholesterol and triglycerides in the blood (Kaplan et al., 1957; Sussman et al., 1958). A similar response was noted to nicotine administration in dogs (White et al., 1964; Kershbaum et al., 1965, 1967a, 1967b). There is also an accompanying elevation of blood glucose related to the release of epinephrine which has a glycogenolytic action (Tsujimoto et al., 1965; Milton, 1966). Hyperlipidemia induced in dogs by nicotine can be prevented by prior injection of adrenergic blocking drugs (Kershbaum et al., 1966). Animals with hypercholesterolemia show an interaction with nicotine. The administration of nicotine and ergonovine produces necrosis in the heart (Wenzel et al., 1961). Grosgogeat did not find lesions in the rabbit aortic wall with nicotine treatment alone (Grosgogeat et al., 1965). There is a diminution in the rate of synthesis of cholesterol in dogs that have been subjected to chronic administration of nicotine (Gudbjarnason, 1968). The relationship of cholesterol to atherosclerotic lesions is discussed in the preceding section.

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X-F. Experimental Thrombosis

The release of epinephrine from the adrenal medulla has been known to increase the coagulability of the blood in vitro (Cannon and Gray, 1914; Cannon and Mendenhall, 1914a, 1914b). More recently, this phenomenon regarding epinephrine has been demonstrated by techniques involving experimental thrombosis (Rosewell et al., 1966) and platelet aggregation (Shimamoto and Ishioka, 1963; Ardlie et al., 1966; Hampton and Mitchell, 1966; Besterman et al., 1967).

That nicotine releases epinephrine does not necessarily mean that all its reported effects on blood coagulation are mediated through this mechanism. Platelet aggregation results from the in vitro addition of nicotine, which must act directly on the cells not containing a significant amount of epinephrine (Werle and Schievelbein, 1965). In the rat, the thrombosis induced by a single subcutaneous injection of carragenine and nicotine can be simulated by substituting epinephrine for the nicotine (Jan et al., 1969). Chronic injection of nicotine in the same animal species caused decreased thrombus formation, indicating that there is no experimental support for the statement that habitual smokers are susceptible to thrombus formation (Wenzel and Richards, 1970). In rats maintained on a hypercholesterolemic diet, the administration of nicotine shortens coagulation time (Singh, 1965).

In other species, nicotine has varied effects, such as: reduction of toxicity of nicotine injected intravenously by increasing the number of platelets by transfusion in rabbit (Schievelbein and Schirren, 1964), decrease of

fibrinolysin in the guinea pig by chronic administration of nicotine (Belli et al., 1965), and nicotine-heparin antagonism when added to human blood in vitro (Singh and Oester, 1964a, 1964b). These observations suggest that nicotine influences coagulability by several mechanisms other than the release of epinephrine.

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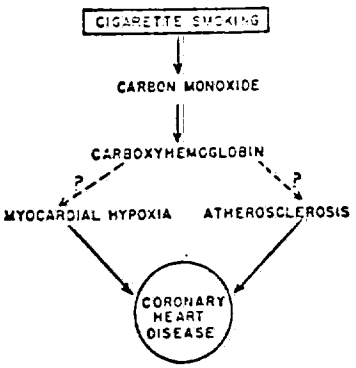
XI. CIRCULATORY EFFECTS OF CARBON MONOXIDE



XI CARBON MONOXIDE

The most important single measurement for assessing the extent of exposure to carbon monoxide contained in cigarette smoke is that of the blood level of carboxyhemoglobin. This form of hemoglobin reduces the availability of oxygen, so that there is a danger of producing generalized hypoxia. It has been suggested that the hypoxia in the myocardium would lead to coronary heart disease and vascular hypoxia to atherosclerosis. The experiments which form the basis of this statement are analyzed in the present section.

The author has completed a separate review entitled "Cigarette Smoking and Carbon Monoxide" and submitted it to the Council for Tobacco Research on January 3, 1973. It contains a discussion of the effects of carbon monoxide as it relates to cigarette smoking. The circulatory effects are recounted in this section and the literature has been updated to July 1, 1973.

XI-A. Carboxyhemoglobin Blood Levels

The carboxyhemoglobin present in the blood is not able to dissociate readily to allow the hemoglobin portion to combine with oxygen. The blood levels are reported for the habitual smoker compared with the nonsmoker, and the acute elevation during cigarette smoking.

1. Habitual smokers compared with nonsmokers. The first identification of carboxyhemoglobin in blood of smokers was accomplished by Hartridge (1919-1920). He estimated the carboxyhemoglobin level in one smoker to be 6% and in another to be absent. A more extensive investigation was completed by Gettler and Mattice (1933), who compared four groups of habitual cigarette smokers. The group of 12 rural dwellers had a mean value of 1.2% carboxyhemoglobin in the blood, while 18 New York City residents had a mean of 1.4%, 12 New York City cleaners a mean of 3.5%, and two New York City taxi drivers a mean of 13.5%. These results proved for the first time that the carboxyhemoglobin contained in blood of habitual smokers was not only the result of cigarette smoking but was also the outcome of inhaling an atmosphere containg carbon monoxide released from automobile exhaust and other sources.

There have been 28 additional reports of carboxyhemoglobin in blood levels among cigarette smokers and the results are summarized in Table XI-A. The mean values do not represent the effect of cigarette smoking because the contribution of carbon monoxide in the atmosphere has to be subtracted. The last column in Table XI-A is the net level of carboxyhemoglobin which can be attributed to cigarette smoking and was obtained by subtracting the mean

blood levels for controls who were nonsmokers. The following generalizations can be made from the published results.

a. The 30 investigations summarized in Table XI-A were performed in various cities in the United States and Europe. The highest mean level is 16.2% for a group of 6 U.S. Army enlisted men (Meigs, 1948). This represents an error in the analysis, since the blood levels for nonsmokers were also high. All the other mean levels were below 10% carboxyhemoglobin.

b. The overall mean level for 2,054 subjects reported in the 30 investigations is 3.76%. This represents the average blood level for smokers in the morning, 4 to 12 hours after they smoked a cigarette.

c. The contribution of atmospheric pollution to the increased blood levels of carboxyhemoglobin can be derived by subtracting the blood levels for controls who were nonsmokers. Twenty-one of the investigations included nonsmokers, so that it was possible to subtract their mean levels from those of habitual smokers. The net difference between 2 groups represents the contribution from smoking alone, which amounted to a mean of +2.19% of carboxyhemoglobin for 2,781 subjects. This mean value was calculated regardless of the number of cigarettes consumed.

d. Ten investigators related the amount of cigarettes consumed daily to blood levels of carboxyhemoglobin. The consumption of 20 or less cigarettes per day showed the following net change in blood carboxyhemoglobin levels in each case: +1.6% (Schmidt, 1939); +2.4% (Schrenk, 1942); +2.1% (Parmeggiani and Gilardi, 1952); +1.0% (Goldsmith et al., 1963); +1.9%

(Curphey et al., 1965) +0.3% (Balbo et al., 1966); and +0.9% (Rouch et al., 1971). The net changes in blood carboxyhemoglobin levels for subjects consuming one or more cigarettes were respectively: +2.9% (Schmidt, 1939); +3.7% (Schrenk, 1942); +3.5% (Parmeggiani and Gilardi, 1952); +1.1% (Goldsmith et al., 1963); +3.6% (Curphey et al., 1965); +2.0% (Balbo et al., 1966); and +8.0 (Yacoub et al., 1970). The last-mentioned value represents the highest net level of carboxyhemoglobin, next to the +11.0% referred to above as reported for the U.S. Army enlisted men.

(Table XI-A appears on the next page.)

Table XI-A. Carboxyhemoglobin levels in the blood of habitual smokers.[1]

Reference (year)	Nature of habitual smokers (Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level %: Smokers Mean ± SD (Range)		Non-smokers Mean	Net
Hartridge (1919-1920)	London volunteers	2	3.0	(0-6)		
Gettler and Mattice (1933)	New York residents	18	1.4	(1.0-4.1)		
	New York street cleaners	12	3.5	(1.2-0.9)		
	New York taxi drivers	2	13.5	(8.0-19)		
	Rural dwellers	12	1.2	(0.5-3.6)		
Ruhl and Lin (1936)	Berlin volunteers					
	(non-inhalers in morning)	21	0.6			
	(inhalers in morning)	25	0.5			
	(heavy inhalers in morning)	13	1.3			
	(heavy inhalers in evening)	13	2.6			
Schmidt (1939; 1940)	Bonn volunteers					
	(20-30/day)	3	3.5		0.6	+2.9
	(>30/day)		7.2			+6.6
	(10-20/day)		2.2			+1.6
	(<10/day)		1.5			+0.9
Schrenk (1942); Sievers, Edwards Murray and Schrenk (1942)	Holland tunnel workders					
	(<20/day	39	4.1 ± 1.9		1.7	+2.4
	(>20/day)	21	5.4 ± 1.8			+3.7
	(pipe)	5	2.5			
	(cigar)		3.2			
Wennesland 1945	Stockholm volunteers					
	(<15/day)	35		(0.5-10.5)		
	(pipe)	7		(0-11.5)		
Meigs 1948	US army enlisted men					
	(6-20/day	6	16.2	(1.9-45)	5.2	+11.0
Parmeggiani and Gilardi (1952)	Italian volunteers					
	(10-12/day)	14	4.9	(1-9)	2.8	+2.1
	(15-25/day)	6	6.3	(2-9.5)		+3.5
	(30-40/day)	3	9.3	(6-14)		+6.5
Barthe, Paris, Duchemin and Thomas (1953)	Paris workers	100		(0.8-2.0)		
Ruel and Barthe (1954)	Paris workers					
	(<10/day)		1.0			
	(10-15/day)		1.7			
	(>20/day)		2.7			
Valic and Duric (1954)	Yugoslavian workers	75	3.8 ± 1.9		0.9	+2.9
Gettler, Cadigan, Wilcott, Jones and Marks (1957)	Boston workers	9	4.7	(3.1-7.9)	0.9	+3.8
Dahlström, Nordström-Öhrberg and Rothschild (1958)	Stockholm volunteers	6	2.1	(1.2-3.0)	0.7	+1.4

Reference (Year)	Nature of habitual smokers (Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level % Smokers Mean ± SD (Range)	Non-smokers Mean	N
Sunder and Harper (1962)	Sunderland volunteers	3	3.8 (3.2-4.8)	0.9	+2.9
Hofreuter, Catcott and Xintaras (1962)	Cincinnati volunteers	19	2.9	1.9	+1.0
Goldsmith, Schuette and Novick (1963)	San Francisco longshoremen				
	(<10/day)	429	2.3	1.3	+1.0
	(10-40/day)	1035	3.4		+1.1
	(>40/day)	233	5.5		+4.2
Curphrey, Hood and Perkins (1965)	Los Angeles longshoremen				
	(light)	55	2.3	0.4	+1.9
	(medium)	153	3.0		+2.6
	(heavy)	29	4.0		+3.6
Ayres, Gianelli and Armstrong (1965)	New York volunteers	25	4.2	0.9	+3.3
Balbo, Marucci and Ronchi (1966)	Paris workers				
	(5/day)	34	2.1 (0-9.8)	1.9	+0.2
	(10/day)	32	2.2 (0-9.5)		+0.3
	(15/day)	16	2.2 (0-5.9)		+0.3
	(20/day)	20	2.2 (0-6.9)		+0.3
	(30/day)	7	2.8 (0-5.2)		+2.0
Levaine, Nelson and Bartlett (1969)	Durham workders	5	3.8	1.6	+2.2
Bhown, Maitrya and Haq (1969)	Indian beedi smokers				
	(<10/day	7	4.8 (3.4-5.6)		
	(10-19/day)	8	5.9 (5.6-6.1)		
	(20-29/day)	8	6.9 (6.6-7.3)		
	(>29/day)	7	9.4 (8.5-10.5)		
Yacoub, Faure, Mallion and Cau (1970)	Paris workers				
	(20/day inhaled)	90	9.5	1.5	+8.0
	(20/day non-inhaled)	97	6.0		+4.5
Rouch, Rioufol and Bourbon (1971)	Toulouse volunteers				
	(<10/day)	5	2.5 (1.0-5.5	1.6	+0.9
	(>10/day)	15	4.25 (1.0-11.0)		+2.6
Brewer, Eaton, Weil and Grover (1970); Brewer, Eaton, Grover and Weil (1971)	Leadville volunteers	20	6.6 ± 2.7		
Weiss, Slawsky and Desforges (1971)	Boston patients with fibrosis	8	4.2 ± 2.7	1.5	+4.2
Sjoy (1971)	Los Angeles residents	81	5.7 (3.2-14.2)	1.5	+4.2
Hansen, Wilke, Malorny and Gothert (1972)	Hamburg workers	40	4.9 ± 1.0	0.75	+4.2

Reference (Year)	Nature of habitual smokers Cigarette consumption)	No. of Subjects	Carboxyhemoglobin blood level %			
			Smokers Mean ± SD (Range)		Non-smokers[2] Net Mean	
[illegible]rson, Garby, [illegible]bert and Zaar (1972)	Uppsala volunteers	6	2.7	(1.5-4.4)	1.27	+1.4
Mean (overall for number of subjects)			3.76 (2954 subjects)			+2.19 (2781 subjec

[1] Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

[2] See Table 4 for details.

XI. CIRCULATORY EFFECTS OF CARBON MONOXIDE

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